REMARKS

The amendments to the claims are supported by the specification at page 16, lines 4-5; page 7, lines 3-7; page 8, lines 2,3, 16, 26-27; page 9, lines 15-16, 22, 23; page 8, lines 31-32; page 10, lines 19, 26-31; page 11, line 22; page 12, lines 12-14 and 29; page 13, lines 9 and 17-20; page 14, lines 18-19; page 15, lines 25-28; page 16, lines 4-5;

Claims 1-37 are pending.

Claim Rejections -- 35 U.S.C. §102

Claims 20-22 and 25 were rejected as anticipated by Geisslinger. Applicants respectfully traverse the rejection.

Geisslinger teaches an ibuprofen composition with improved tablettability, strength and liberation (column 2, lines 35-39). The composition is made by dry mixing 100 parts by weight of ibuprofen with about 50-150 parts by weight of calcium compounds, such as $CaCO_3$ and $CaHPO_4$ (column 2, lines 44-48). The composition can contain a wetting agent, e.g. sodium lauryl sulfate, Tween, and sodium dioctyl sulfosuccinate, as well as additional usual adjuvant or carrier materials (column 3, lines 20-26). Geisslinger's composition fails to anticipate claims 20-22 and 25 because Geisslinger's composition contains no carbonate or bicarbonate of an alkali metal, i.e. no carbonate or bicarbonate of an element of Group I of the Periodic Table. Thus, Geisslinger fails to teach every limitation of the rejected claims. Applicants note that the term "alkali metal" does not include calcium.

Claims 20-22 and 25 further differ from Geisslinger in that Geisslinger does not teach compressing the mixture into a solid dosage form having a crushing strength in

the range of 6.5-15 Kp.

Withdrawal of the anticipatory rejection is requested.

Claim Rejections -- 35 U.S.C. §103

I. Claims 1-8, 10-13, 16-18, 20-22, and 24-26 were rejected as obvious over Geisslinger in view of Gregory (US 5,262,179) and further in view of Elger (US 4,844,907). Applicants respectfully traverse the obviousness rejection.

The Office Action asserts that Geisslinger teaches all of the limitations of the claims, but applicants submit that the Office Action's assertion is wrong. This is because the Office Action already acknowledges that Geisslinger does not teach the crushing strength of the tablets, sodium carbonate or bicarbonate, and the ratios recited in the claims.

Furthermore, claim 1 has been amended so that claim 1 requires

(i) that the compressed dosage form is suitable for oral administration;

(ii) that the ibuprofen medicament is in a racemic form;

(iii) 3 – 20% solid alkali metal carbonate or bicarbonate in the formulation; and

(iv) that the alkali metal carbonate or bicarbonate is in homogeneous admixture with the ibuprofen and the filler/disintegrant.

Geisslinger discloses that problems encountered in making ibuprofen tablets are known in the art (column 1, lines 15-48). Geisslinger seeks to improve tablettability by using approximately equimolar quantities of calcium compounds in addition to the ibuprofen medicament (columne 2, lines 28-29). In order to accommodate the amount of calcium compound required in Geisslinger's formulation, the calcium compound must

also be capable of compression into a tablet. In contrast, the claimed invention relates to the addition of small quantities of sodium carbonate or bicarbonate with any compressible filler.

The Office Action attempts to rely on Gregory and Elger to cure the deficiencies of Geisslinger.

Gregory concerns a way to deal with ibuprofen's disadvantage of a poor taste. The poor taste is not a significant problem for tablets for oral administration, such as those of the claimed invention, because the tablet is swallowed rapidly. However, the poor taste of ibuprofen is a considerable problem in preparing acceptable liquid formulations. Gregory is primarily directed to the masking of the taste of ibuprofen in liquid formulations by adding an alkali metal bicarbonate (see Abstract; column 2, line 62 to column 3, line 13). Gregory teaches the provision of sachets of loose powdered materials (column 4, lines 3-5). The alkali bicarbonate in the sachet will mask the taste of ibuprofen when the sachet is poured into water, so ibuprofen is administered in a liquid formulation according to Gregory.

Because Gregory's sachet formulations are aimed to be added into water, there is no practical limit on the amounts of excipients as in the formulation of ibuprofen tablets suitable for oral administration defined in the instant claims. In comparison, in preparing ibuprofen tablets for oral administration, it is usually desired to incorporate 200 mg ibuprofen into the dosage form. However, one of ordinary skill in the art knew that the practical limit of the weight of the tablet for oral administration is about 700 mg total tablet weight. This is consistent with the disclosure of the present application which requires the ibuprofen to form at least 35% w/w of the tablet for oral

adminstration. The ibuprofen tablets prepared in the working examples of the present application have a total tablet weight of less than 700 mg. In contrast, all the working examples of Gregory prepared sachet formulations having a total weight of 1301 mg to 2828 mg. The amount of ingredients in Gregory's sachets is too much to be practical for producing an ibuprofen tablet for oral administration. There would have been no motivation to use the teachings of Gregory to modify the ibuprofen tablets of Geisslinger.

The Office Action asserts that Gregory teaches powder compositions of the sodium salt of ibuprofen (column 3, lines 26-27) and sodium bicarbonate (abstract) that may be formulated into tablets (column 4, lines 3-6). The Office Action relies on Elger for the teaching of a layered tablet containing ibuprofen in a layer.

The Office Action states that the ibuprofen composition of Gregory can be in the form of a tablet (column 4, lines 3-6). However, any such tablets produced are arranged to be added to water for adminstration in a liquid form, so there is no motivation to reduce the amount of excipient included. Therefore, ibuprofen tablets produced in accordance with the teachings of Gregory would be unacceptably sized for a tablet adapted to be swallowed. Furthermore, they are not particularly formulated to have satisfactory disintegration characteristics for release in the gastro-intestinal tract.

Claim 1 requires that ibuprofen be present at 35% or more of the dosage form. In contrast, the formulations of Gregory contain significantly less ibuprofen than required by claim 1 due to the amount of additional ingredients used. Neither is there any teaching in Gregory that the ingredients should be present in an orally administerable compressed dosage form having the crusing strength and disintegration characteristics

specified in claim 1.

Accordingly, one of ordinary skill in the art would not use the sodium salt of ibuprofen with sodium bicarbonate in liquid dispersible formulations (containing large amounts of excipients arranged to give an acceptably tasting liquid) as disclosed by Gregory, in Geisslinger's tablet (which requires the presence of substantial amounts of calcium compounds) which has to be of acceptable size to be swallowed. Thus, claim 1 should not be obvious over Geisslinger in view of Gregory.

Elger does not cure the deficiencies of Geisslinger in view of Gregory. Elger discloses ibuprofen in a layered tablet, however, Elger does not suggest that an alkali metal carbonate or bicarbonate should be included in the ibuprofen layer. In view of the above discussion, modifying Geisslinger in view of Gregory with the further knowledge contained in Elger does not render the subject matter of claim 1 obvious.

Withdrawal of the obviousness rejection is requested.

II. Claims 1-26 were rejected as obvious over Geisslinger in view of Birrenbach (US 5,631,296) and further in view of Denton (WO 89/022266). Applicants respectfully traverse the rejection.

Birrenbach teaches a composition of S(+)-ibuprofen and sodium carbonate or potassium carbonate (column 3, lines 11-13, 32-41 and 47-48).

As noted above, claim 1 has been amended. The four limitations discussed above also provide a distinction over Birrenbach.

The present claims are restricted to the compression of racemic ibuprofen medicaments into tablets whereas Birrenbach is solely directed to the problems of

providing pellets of S(+)-ibuprofen capable of being formulated into tablets. Racemic ibuprofen and S(+)-ibuprofen are distinct materials. Not only do they have different melting points S(+)-ibuprofen has a melting point of about 55°C and racemic ibuprofen has a melting point of about 76°C), but they have some differences in the pharmacology of their action, particularly with regard to onset of analgesic activity. This is discussed at columns 1 and 2 of Birrenbach (especially column 1, lines 47-66).

Furthermore, Birrenbach relates to the production of quickly disintegrating S(+)-ibuprofen tablets which contain a high percentage of S(+)-ibuprofen wherein the S(+)-ibuprofen has been formed into rounded pellets which are capable of having a coating applied thereto which provides desired tabletting and release characteristics (see US 5631296, column 4, line 15 onwards). According to the disclosure at column 3, lines 34-38 of Birrenbach, it has been found that the addition of small amounts of a basic salt or base make it possible to form pellets containing a high concentration of S(+)-ibuprofen which release the active substance very quickly. At column 4, lines 6-12 Birrenbach discloses that the pellets can be prepared by spraying the mixture containing S(+)-ibuprofen and at least one further adjunct (eg microcrystalline cellulose, lactose, HPMC and/or silicon dioxide (see column 3, lines 52-55)) in a rotary processor or Diosna mixer with a basic inorganic salt in aqueous solution or with a dilute alkali metal hydroxide solution. The rounded pellets formed are dried. The S(+)-ibuprofen pellets may be coated and are then combined with tabletting auxiliary materials prior to tabletting. A list of tabletting auxiliaries with which the S(+)-ibuprofen pellets may be mixed is provided at column 5, lines 42-63 of Birrenbach. It does not disclose the incorporation of sodium carbonate or bicarbonate as a tabletting auxiliary.

In contrast, the present invention does not require the complicated processing stage of Birrenbach in which the S(+)-ibuprofen has to be formed into pellets (formulated in combination with a small amount of inorganic metal salt or alkali metal hydroxide). Examples 8 and 9 of Birrenbach disclose tablets containing 63% coated pellets and 37% auxiliary tabletting materials. Examples 1 and 2 are the only illustrative Examples which show the use of sodium carbonate in the S(+)-ibuprofen pellets and teach that it is used in an amount of 2% w/w of the pellet. Accordingly, the incorporation of these pellets into the Examples 8 and 9 tablets provide that the amount of sodium carbonate is less than 1.5% w/w of the tablet. In contrast, the claimed invention requires 3-20% solid alkali metal carbonate or bicarbonate.

These Examples are in line with the text of Birrenbach at column 3, lines 44-46, which states that the preferred pellets contain 96.0-98.0% by weight, especially 97% w/w S(+)-ibuprofen and 1.0-3.0% by weight, especially 2% by weight of a basic inorganic salt or a dilute alkali metal hydroxide solution. The proportion of basic inorganic salt in the whole formulation is further reduced by the addition of preferably 240-260mg, particularly preferably 250mg, of at least one tabletting auxiliary for 400mg of S(+)-ibuprofen (corresponding to 62% S(+)-ibuprofen pellets and 38% tabletting auxiliaries). Claim 1 of the present application specifies that the dosage form comprises 3-20% w/w alkali metal carbonate or bicarbonate in contrast to the above disclosure of Birrenbach. This is one of the reasons why the instant claims should not be obvious.

Furthermore, claim 1 requires that the alkali metal carbonate or bicarbonate is in homogeneous mixture with both the racemic ibuprofen medicament and also with the compressible filler with disintegrating component. In Birrenbach, the tablets comprise

pellets containing a small amount of sodium carbonate (eg 2% w/w) and optionally other adjuncts (less than 5%) combined with over 90% w/w S(+)-ibuprofen, which pellets are surrounded by auxiliary tabletting material, ie the auxiliary tabletting material fills the interstices between the pellets. Accordingly, Birrenbach does not teach a homogeneous combination of the sodium carbonate with the medicament and the compressible filler component with disintegrating component. This is another reason why the instant claims should not be obvious.

Accordingly, it is submitted that one of ordinary skill in the art would not combine

a) the disclosure relating to producing pellets of S(+)-ibuprofen (with very small amounts of sodium carbonate to aid release of the very high percentage of S(+)-ibuprofen from the pellets) which are capable of being coated to provide desired release properties and which are tabletted with conventional auxiliary tabletting materials, with

b) the calcium compound-containing 2-arylpropionic acid tablets of Geisslinger,

to arrive at the homogeneous mixture of ingredients in the amounts specified and having the crushing strength and disintegration time characteristics contained in claim 1.

Accordingly, claim 1 should not be obvious over Geisslinger in view of Birrenbach and further in view of Denton.

Denton achieves satisfactory tablets by spraying an aqueous dispersion of a starch binder onto a fluidized powder comprising ibuprofen and a portion of the carboxymethylcellulose in a fluidized bed granulator-dryer, drying the resulting granules to a particular moisture level and thereafter blending a lubricant and the remaining portion of the carboxymethylcellulose.

It is submitted that the simple mixture of widely available materials specified in

claim 1 of the present application is not disclosed or suggested by Denton and therefore is not rendered obvious in view of Denton and Geisslinger. The Office Action even acknowledges that Denton does not teach an alkali metal metal carbonate or bicarbonate and a salt of ibuprofen.

Regarding the rejection of claim 11, the same comments apply as above, particularly that the amounts taught by Gregory would not lead a person skilled in the art to combine a calcium compound-containing orally administered tablet of Geisslinger with the dispersible sachet formulations of Gregory to arrive at a solid dosage form according to the present invention.

Claim 11 is further distinguished from Birrenbach in view of the disclosure that the Birrenbach S(+)-ibuprofen pellets can be prepared by spraying the mixture containing S(+)-ibuprofen (and at least one adjunct) in a rotary processor or Diosna mixer, with a basic inorganic salt in aqueous solution or with a dilute metal hydroxide solution (emphasis added). Claim 11 requires that the carrier material comprising the alkali metal carbonate or bicarbonate is mixed with the ibuprofen medicament under dry conditions. It is considered undesirable to combine ibuprofen under wet conditions with significant amounts of a carbonate or bicarbonate as there may be sufficient of an interaction between these components to form a salt to affect the properties of the resulting tablet. The small amount of sodium carbonate relative to the S(+)-ibuprofen and the special pelleting processing conditions of Birrenbach may explain why these ingredients can be combined under wet conditions. However, the technology of Birrenbach is thus clearly distinguished from the simple mixtures according to the present invention. This is another reason why claim 11 would not have been obvious.

Withdrawal of the obviousness rejection is requested.

Conclusion

With the above amendments and reasoning, applicant respectfully submits that the application is in a condition for allowance.

In case this paper is not timely filed, the undersigned hereby petitions for an appropriate extension of time. In the event that any fees are due in connection with this paper, please charge our Deposit Account No. 01-2300.

Respectfully submitted,
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